Progress in feline diabetes: keys to achieve diabetic remission

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Remission of diabetes is defined as a situation in which clinical signs of diabetes disappear, blood glucose concentration normalizes and insulin treatment can be discontinued. In human medicine, the duration of normoglycemia has to be at least one year to be labelled remission (Buse et al, 2009). In cats, there is not yet an agreement of the time period. In Zurich we use a cut-off of 4 weeks as criterion, i.e. the disease-free interval has to last for a minimum of 4 weeks before the diabetes is considered to be in remission (Sieber-Ruckstuhl et al, 2008; Zini et al, 2010; Tschuor et al, 2011; Hafner et al, 2014; Zini et al, 2015). The first study on cats which had experienced diabetic remission was published by Nelson et al in 1999, at that time the phenomenon was called "transient diabetes". Interestingly, at the time of diagnosis of the diabetes in those cats, baseline insulin concentrations were undetectably low or within the reference range and did not increase after IV glucagon administration, mimicking type 1 diabetes. A second glucagon test, performed after remission had occurred, showed an immediate and significant increase in insulin concentration similar to test results in healthy cats. Histological evaluation of the pancreas revealed decreased numbers of islets, islet amyloidosis and vacuolar degeneration of islet cells. This study demonstrates that initial insulin secretion is severely impaired even in cats with the potential of remission, and that the glucagon test performed at the time of diagnosis is not helpful to predict remission. The study also showed, that cats experiencing diabetic remission are not "cured", as they have islet cell pathology. The vast majority of cats in diabetic remission has impaired glucose tolerance and severe impairment of glucose tolerance is associated with relapse of diabetes (Gottlieb et al 2015). Remission is increasingly recognized and it is well accepted that good glycemic control improves β-cell function leading to diabetic remission in a substantial percentage of cats. Treatment may lead to improvement of β-cell function, most likely due to abolishment of the damaging effects of high blood glucose on β-cell function (glucotoxicity). Those cats most likely have a type 2 like diabetes resulting from insulin resistance and β-cell dysfunction and some degree of β-cell loss. Their remaining β-cells, however, have the capacity to recover, at least in part, during treatment. Cats which do not experience diabetic remission may be in a more advanced stage of their disease with more pronounced β-cell loss. Alternatively, those cats may suffer from concurrent disease, for instance chronic renal failure or pancreatitis, which renders glycemic control difficult and may make remission impossible. In 10 – 15% of diabetic cats the disease is caused by hypersomatotropism (acromegaly) and in those cases, remission is unlikely. Diabetic remission most often occurs during the first three to four months of therapy. Consequently, the first months after diagnosis is the most important time

during management of diabetes in cats and therapy should be started without delay. Remission rate is low when oral hypoglycemic agents (i.e. glipizide) are used as the sole agent and therefore, insulin is the preferred medical therapy with the highest chance of diabetic remission. It is currently believed that remission rates are higher when cats are treated with newer types of insulin (e.g. insulin analogues such as glargine or determir) than with older types of insulin (e.g. lente type) (Marshall et al, 2009; Roomp and Rand, 2009; Roomp and Rand, 2012). For instance in two recent studies, using insulin glargine and determir respectively, overall remission rates of 64% and 67% were achieved (Roomp and Rand, 2009; Roomp and Rand, 2012). Those studies, however, used an extremely intensive treatment and monitoring protocol: glucose targets were set very low (50 – 200 mg/dl and 50 – 100 mg/dl respectively; 2.8 – 11.1 mmol/l, 2.8 – 5.5. mmol/l), the owners had to measure blood glucose at home at least three times daily and adapt the insulin dosage accordingly. Another study found that in cats in which insulin dosing was based on maintaining blood glucose between 60 and 160 mg/dl (3.3 and 8.8 mmol/l), remission was seen significantly more often compared to cats in which insulin dosing was based on clinical signs (Nack and DeClue, 2014). Those treatment protocols can only be used under very close supervision, as there is an increasing risk of hypoglycaemia the lower the glucose targets are set. The overall reported remission rate in studies using insulin glargine (Lantus) is 47.6% (Gostelow et al, 2014). The AAHA diabetes management guidelines recommend to use insulin glargine (Lantus) or PZI (ProZinc) as initial insulins of choice (Rucinsky et al, 2010), the recent ISFM guidelines recommend the same two types of insulin as well as insulin detemir (Levemir) (Sparkes et al, 2015). Although duration of action is quite long (> 12 hours) those three insulins should be injected twice daily for optimal glycemic control. Diet is an important component of the treatment plan. There is current agreement that a high-protein-low carbohydrate diet should be fed, the AAHA guidelines recommend to feed a diet with the lowest carbohydrate content the cat will eat. Wet food is preferred over dry food as it provides lower carbohydrate levels, lower energy density and additional water intake. In case of obesity, calories should be restricted to achieve 1- 2% weight loss per week (Rucinsky et al, 2010). According to Bennet et al (2006) remission rate is higher in cats fed a low-carbohydrate diet compared to cats fed a diet with moderate carbohydrate content.
As shown by Nelson et al (1999), no difference in insulin response during glucagon test was seen in cats with and without remission. Studies in humans have demonstrated that the first defect in the early phase of diabetes is a loss response to IV glucose, followed by a loss of response to IV glucagon, whereas response to arginine persists the longest. It was, therefore, hypothesized that cats, which experience remission at some time after starting treatment, have less severe β-cell defects than cats with permanent disease and would therefore show normal or at least some degree of insulin response after IV arginine. However, the expectations were not met. In both groups of cats (remission and no remission) insulin concentrations increased mildly after IV arginine, but there was

no significant difference between the two groups, similar to what has been shown with the glucagon test (Tschuor et al, 2011). Therefore, none of the tests used so far allows discrimination between cats with and without the chance of remission. Long duration of diabetes, presence of diabetic polyneuropathy, hypercholesterolemia and clearly increased fPLi seem to be associated with a lower chance of diabetic remission (Roomp and Rand, 2009; Zini et al, 2015). In contrast, cats which developed the diabetes after glucocorticoid therapy have a good chance to experience remission. In one of our studies we found that remission was more likely with older age (Zini et al, 2010). Interestingly, diabetic ketoacidosis has not been identified as a negative predictive factor and remission may also occur in cats presented with diabetic ketoacidosis (Sieber-Ruckstuhl et al, 2008). In many cats, remission lasts for months to years and may even be life-long. Roughly 30% of cats with remission will have a relapse with recurrence of clinical signs and hyperglycemia and will again require insulin therapy. In some of them, a second remission is possible, more often, however, permanent insulin therapy is required.

In our own institution remission rate has varied between 40 and 50% over the years under the following conditions: cats are newly diagnosed with diabetes and have no severe concurrent diseases (e.g. heart failure, renal failure, severe pancreatitis, hypersomatotropism), they are treated according to a standardized insulin treatment protocol, fed a low-carbohydrate-high-protein diet and are frequently re-evaluated during the first 4 months of therapy. We do not follow an aggressive remission protocol, because our primary aim is to control clinical signs of diabetes and to avoid hypoglycaemia. Our insulins of first choice are insulin glargine (Lantus) or PZI (ProZinc). In cats $\leq$ 4 kg body weight starting dose of insulin glargine usually is 1 U/cat BID, in cats > 4 kg 1.5 U/cat. When PZI is used starting doses usually are 0.5 U/cat higher (1.5 U/cat and 2 U/cat). A high-protein-low-carbohydrate diet (Purina DM) is highly recommended to all owners. During the initial visit a thorough work-up is performed including routine laboratory evaluation and abdominal ultrasonography and concurrent disease are treated whenever possible. As a minimum, re-evaluations are scheduled after 1, 2, 6, 10 and 16 weeks, some cats need additional appointments. Re-evaluations include a thorough history, physical examination, generation of a blood glucose curve (measurement of blood glucose every 2 hours) and measurement of fructosamine. The owners are introduced to home-monitoring of blood glucose after 1 – 2 weeks. Home-monitoring allows more frequent blood glucose measurements and more frequent amendments of the insulin dose. Additionally, measurements are not influenced by the stress of hospitalisation. For the initial treatment period (first 3 to 4 months) we recommend that owners measure the fasting blood glucose at least twice per week and generate a blood glucose curve once per week (e.g. on Sundays). The highest blood glucose should not exceed 10 and 15 mmol/ (180 - 270 mg/dl) and the glucose nadir should be between 4.5 and 7.8 mmol/l (80 and 140 mg/dl). When blood glucose curves are

generated at home we aim for the lower glucose target (i.e. 10 mmol/180 mg/dl and 4.5 mmol/l/80 mg/dl), when the curves are generated in the hospital we allow the higher end of the glucose targets. Dose titration is done in steps of 0.5 U/cat every 5 to 7 days, except in case of hypoglycemia where a more pronounced and more frequent dose reduction may be necessary. A blood glucose curve should be generated before each dose change. Some investigators advertise a more aggressive treatment protocol with lower glycemic targets, in particular a lower glucose nadir (see above). The most recent ISFM guidelines, however, recommend to avoid a glucose nadir < 4.5 mmol/l (80 mg/dl). If the glucose nadir is in the desired range, but duration of insulin effect is less than 8 – 10 hours, the cat should be switched to a longer acting insulin (e.g. switch from insulin glargine to insulin detemir or PZI).

In cats, in which all blood glucose measurements of a blood glucose curve range between 4.5 – 6.7 mmol/l (80 and 120 mg/dl) and fructosamine is < 350 µmol/l, we start to reduce the insulin dose in steps of 0.5 U/cat BID every 5 – 7 days (Reusch, 2015). The owner is advised to monitor the cat closely with regard to re-appearance of clinical signs and a glucose curve is performed prior to each reduction step. The insulin is reduced until a dose of 0.5 U/cat BID is reached, thereafter, the last step is to reduce insulin dose to 0.5 U/cat SID; if the blood glucose is still normal, insulin administration is stopped. Close clinical monitoring and regular glucose measurement (e.g. fasting blood glucose twice per week) are recommended to ensure that there is no relapse of the disease. Most cats are well regulated or experience diabetic remission with insulin doses < 1. U/kg BID. The higher the insulin requirement, the more likely a concurrent disease is present causing insulin resistance. In those cases, further work-up should be pursued.

In summary, important factors to increase the likelihood of diabetic remission are:
early diagnosis, immediate start of therapy with insulin glargine, insulin detemir or PZI, dietary management with a high-protein-low carbohydrate diet, close monitoring and adjustment of insulin dose based on clinical signs and blood glucose measurements.

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